The Gene for Naegeli–Franceschetti–Jadassohn Syndrome Maps to 17q21

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Naegeli–Franceschetti–Jadassohn syndrome is a rare autosomal dominant form of ectodermal dysplasia affecting sweat glands, nails, teeth, and skin. We have studied a multigeneration family of Anglo-Saxon British descent using microsatellite markers to screen candidate loci, including the epidermal differentiation complex on 1q, the keratin gene clusters on chromosomes 12q and 17q and the desmosomal cadherin gene cluster on chromosome 18q. Significant genetic linkage to chromosome 17q was observed using marker D17S1787, with a maximum two-point LOD score of 4.166 at a recombination fraction of $\theta = 0$. Recombination events in the family place the gene in a 26.97 cM interval between markers D17S798 and D17S957, a region known to contain the type I keratin gene cluster and other genes expressed in epithelia. Keratins K15, K19, and K20, plakoglobin, and MEOX1 were excluded as candidates by direct sequencing of genomic polymerase chain reaction products. ***Key words: ectodermal dysplasia/fingerprints/skin. J Invest Dermatol 115:694–698, 2000***

The Naegeli–Franceschetti–Jadassohn (NFJ) syndrome (MIM 161000) is a rare autosomal dominant form of ectodermal dysplasia affecting the sweat glands, skin, nails, and teeth with a population incidence of approximately 1 in 2,000,000. The syndrome was first described in a Swiss family by Naegeli in 1927 (Naegeli, 1927) with further analysis by Franceschetti and Jadassohn in 1954 (Franceschetti and Jadassohn, 1954), and Itin and colleagues in 1993 (Itin *et al*, 1993). The main symptom in affected individuals is heat intolerance caused by diminished sweating, which can lead to collapse after mild exercise. NFJ syndrome is also characterized by a lack of dermatoglyphics (fingerprint lines) and by a brown reticulate pigmentation of the neck, chest, and abdomen that begins in early childhood (3 mo–6 y) and decreases after puberty, often remitting completely after 60–80 y of age. In addition, spotty pigmentation may be present around the eyes and mouth. Affected individuals also display mild palmoplantar hyperkeratosis, brittle fingernails, and defective dentition with yellow spots on the enamel (Naegeli, 1927; Franceschetti and Jadassohn, 1954; Sparrow *et al*, 1976). In some cases there is also malalignment of the great toenails. A number of other NFJ families have been described that differ slightly in clinical phenotype (Levi *et al*, 1971; Papini, 1978) and intrafamilial variability has also been reported (Itin *et al*, 1993).

To date, the gene for the NFJ syndrome is not known and no genetic linkage studies have been reported; however, several recent mutation analyses have demonstrated the relevance of a number of structural skin proteins to other ectodermal dysplasias and related disorders. For example, mutations in the genes encoding differentiation-specific keratins K6a, K6b, K16, and K17 underlie autosomal dominant forms of pachyonychia congenita (Bowden *et al*, 1995; McLean *et al*, 1995; Shamsher *et al*, 1995; Smith *et al*, 1998) and mutations in the desmosomal plaque protein, plakophilin 1, lead to an autosomal recessive form of hypohidrotic ectodermal dysplasia (McGrath *et al*, 1997). Therefore, several genes encoding keratins and structural components of desmosomes are plausible candidates for the NFJ syndrome.

In this study we present linkage analysis of the British family originally reported by Sparrow *et al* (1976) in order to identify the chromosomal region containing the NFJ locus. We report the mapping of the NFJ syndrome to 17q21 and exclude the type I keratins K15, K19, and K20, plakoglobin, and the MEOX1 gene by direct sequencing.

PATIENTS AND METHODS

Clinical findings A single family of British origin with 25 individuals affected by the NFJ syndrome was studied. Members of the kindred were examined by one of the authors (JAM). The inheritance pattern of NFJ syndrome in the family was consistent with autosomal dominant mode of inheritance, exhibiting male-to-male transmission, as seen in **Fig 1**. Affected family members presented with reticulate pigmentation of the neck, brittle nails, heat intolerance, lack of dermatoglyphics (**Fig 2**), and focal acral hyperkeratosis. Blood samples were available from 13 affected and five unaffected family members. Genomic DNA was extracted from peripheral blood lymphocytes using standard methods.

Genotyping and linkage analysis Microsatellite markers were chosen from the Généthon and Marshfield Genetic linkage maps (Dib *et al*, 1996; Broman *et al*, 1998). Markers D1S305 and D1S498 were used for the epidermal differentiation complex on 1q, markers D12S90 and D12S96 were used for the type II keratin gene cluster on chromosome 12q, markers

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Abbreviation: NFJ, Naegeli–Franceschetti–Jadassohn.

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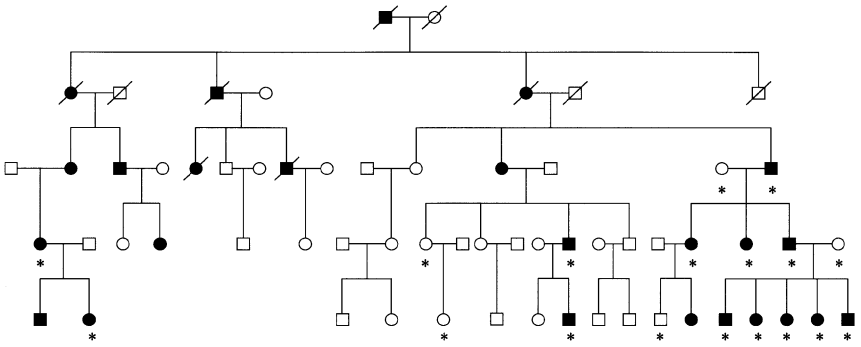

Figure 1. Pedigree of the family with autosomal dominant NFJ syndrome analyzed in this study. There are 25 affected individuals and 37 unaffected individuals. Family members included in this study are indicated by an asterisk (*).

D17S800 and D17S1787 were used for the type I keratin gene cluster on chromosome 17q, and markers D18S463 and D18S536 were used for the desmosomal cadherin gene cluster on chromosome 18q. Polymerase chain reaction (PCR) reactions were performed in 7.5 μl containing 100 ng of template DNA, 1 × GeneAmp PCR buffer II (Perkin-Elmer, Foster City, CA), 330 nM of each primer, 250 μM dNTPs, 2.5 mM $MgCl_2$, and 0.30 units of Amplitaq Gold DNA polymerase (Perkin-Elmer) in a Touchdown ThermoCycler (Hybaid, Ashford, U.K.). One of the two primers was labeled at the 5′ end with fluorescent FAM, HEX, or NED dyes (Perkin-Elmer). Microsatellite DNA marker analysis was performed on either an ABI377 or ABI310 automated DNA sequencer running Genescan software (Perkin-Elmer). Two-point LOD scores were computed using Cyrillic version 2.1.3 (Cherwell Scientific Publishers Ltd, Oxford, U.K.) running the MLINK algorithm of LINKAGE version 5.1. The mutant allele frequency was assumed to be 0.001 with 100% penetrance. Allele frequencies were assumed to be equal in the population. Recalculation of the data for the most significantly linked markers, D17S1787 and D17S1868, giving the linked allele in each case a frequency of 50%, yielded the same LOD scores.

Candidate gene analysis Primers and conditions used to amplify the K15 and K19 genes, the plakoglobin gene, and the MEOX1 gene were as previously described (Futreal *et al*, 1994; Whittock *et al* 2000a,b). Primers to amplify K20 were based on the published gene sequence (GenBank accession no. X73501). For PCR, 200 ng of patient or control genomic DNA was added to a premix containing PCR buffer [67 mM Tris–HCl pH 8.8, 16.6 mM $(NH_4)_2SO_4$, 1.5 mM $MgCl_2$, 0.17 mg per ml bovine serum albumin (Sigma, Poole, U.K.), and 10 mM 2-mercaptoethanol], 10 nmol of each dNTP, and 20 pmol of each primer in a total volume of 50 μl. After an initial denaturation at 95°C for 2 min, 2.5 units of Taq polymerase (Promega, Madison, WI) was added followed by 35 cycles of 94°C for 10 s, annealing for 10 s, 72°C for 30 s, with a final incubation of 72°C for 5 min. The PCR products were examined by 3% agarose gel electrophoresis, purified using spin columns (Qiagen, Crawley, U.K.) and directly sequenced using Big Dye terminators on an ABI 310 genetic analyzer (Perkin-Elmer).

Electronic database information Accession numbers and URLs for data in this article are found in **Table I**.

RESULTS

The NFJ syndrome gene is located on 17q21 DNA was prepared from 18 family members, including 13 affected individuals, and tested for genetic linkage using a panel of microsatellite markers located near candidate genes involved in the structure and/or development of epithelial tissues. Markers located on chromosomes 1q, 12q, and 18q were excluded for linkage to the disease, thereby indicating that the gene for NFJ syndrome was not located in the epidermal differentiation complex, the type II keratin cluster, or the desmosomal cadherin cluster, respectively (data not shown). In contrast, highly significant linkage was seen with a number of markers located in the vicinity of the type I keratin gene cluster on chromosome 17q21, as shown in **Table II**. Maximum two-point LOD scores of 4.166 and 3.717 at $\theta = 0$ were obtained for the markers D17S1787 and D17S1868, respectively (**Table II**). Visible recombination events in the family excluded the NFJ syndrome gene from the region centromeric to D17S798 and telomeric to D17S957. Hence, the genetic defect in this family is located between the microsatellite markers D17S798 and D17S957, which are separated by approximately 26.97 cM, based on the current Marshfield Comprehensive Genetic Map (**Fig 3**).

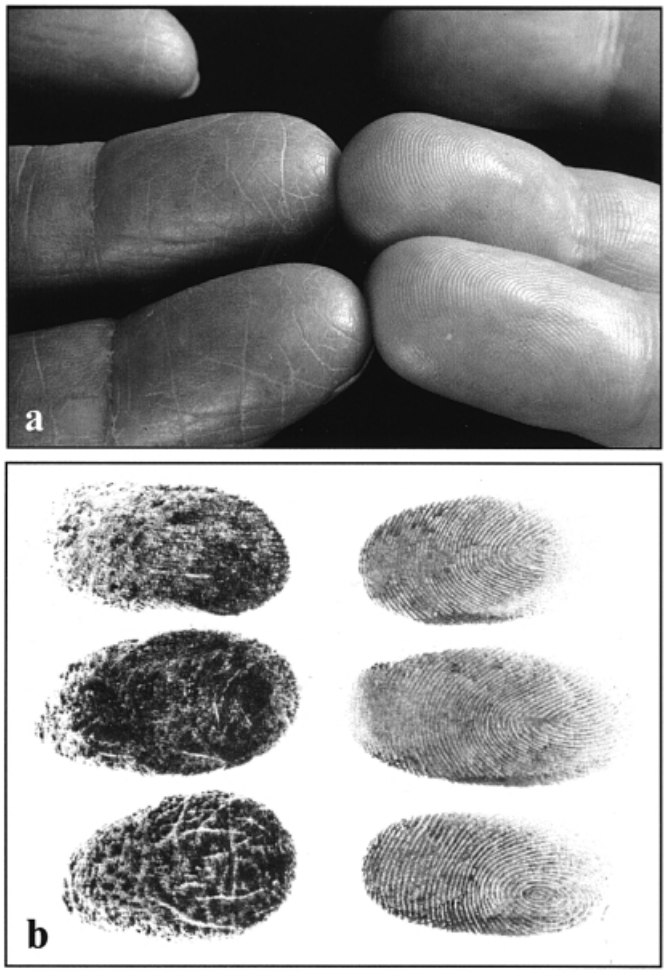

Figure 2. The most striking clinical feature in NFJ syndrome is a complete loss of dermatoglyphics (fingerprint lines). (*a*) The finger tips of an affected individual (left) contrast with an unaffected control (right). (*b*) Indian ink staining of the fingerprint lines shows normal whorls and spirals in the control (right), but only random irregularities in the affected individual (left) corresponding to sites of minor clinical fissuring (as seen in *a* left).

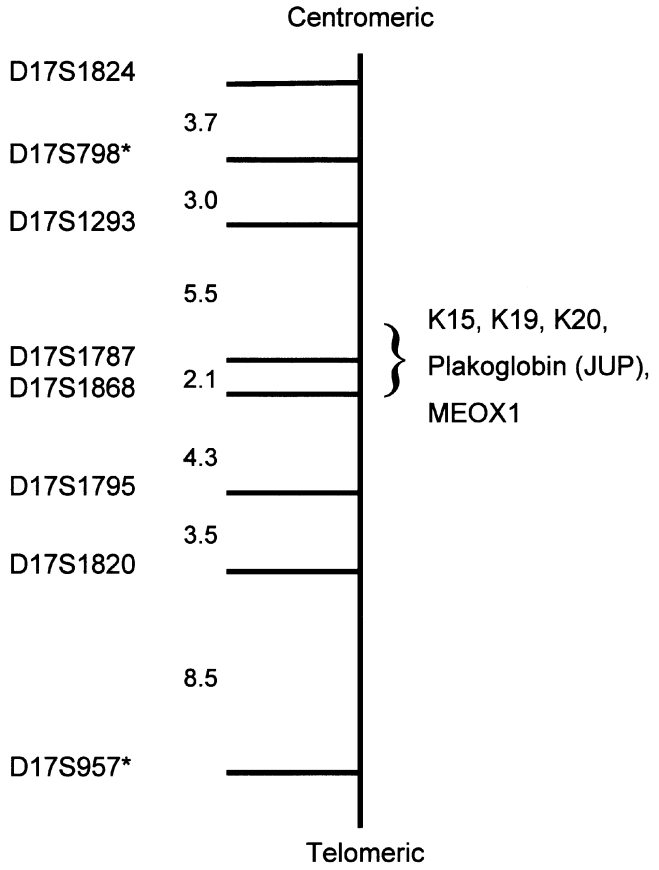

Figure 3. Part of the microsatellite linkage map for chromosome 17q that includes the NFJ syndrome locus. Recombination places the NFJ syndrome gene within markers D17S798 and D17S957 (*). The positions of the candidate genes excluded in this study are indicated. Sex-averaged genetic distances between adjacent markers in centiMorgans from the Marshfield Genetic Map.

Exclusion of cytokeratins, plakoglobin, and MEOX1 in the NFJ syndrome According to the current radiation hybrid map of the human genome, there are several potential candidate genes located between D17S798 and D17S957, namely the type I keratin gene cluster, plakoglobin, and the MEOX1 gene (Froelich *et al*, 1999). The proteins encoded by these genes are involved in the structure and/or development of epithelial tissues. All but three of the known type I cytokeratin genes at this locus have been assigned to other genetic disorders, the exceptions being keratins K15, K19, and K20. Using PCR amplification of DNA followed by direct sequencing, we screened the exons and splice sites of the five candidate genes. No pathogenic mutations were discovered, but several polymorphisms were found that confirmed linkage to this region (data not shown).

DISCUSSION

NFJ syndrome is a rare form of autosomal dominant ectodermal dysplasia. In this report we characterized a large British family affected by this disorder and localized the causative defect to a 26.97 cM region on chromosome 17q21 (**Table II**). Additional markers in the region were uninformative for the recombinants in the family and therefore additional families must be sought to help limit this wide interval. The 17q21 region is known to contain the type I keratin gene cluster of which keratins K15, K19, and K20 have not been assigned to a disease. Therefore, these genes along with the gene encoding the constitutive desmosome and adherens junction protein plakoglobin, and the *MEOX*1 gene, were considered reasonable candidates in the search for the genetic defect underlying the NFJ syndrome in our family. These genes, however, have been excluded as no pathogenic mutations could be found following direct sequencing of all coding regions and intronic splice sites.

Considerable advances have been made in understanding the molecular basis of other forms of ectodermal dysplasia. First, in the X-linked recessive form of hypohidrotic ectodermal dysplasia, mutations were identified in the ED1 gene, encoding ectodysplasin-A (Kere *et al*, 1996). More recently, several autosomal dominant and autosomal recessive cases of ectodermal dysplasia have been shown to result from mutations in the human DL homolog

Table I. Accession numbers and URL for data in this study

CEPH-Généthon Genetic Linkage Map	http://www.genethon.fr.genethon_en.html
GenBank Entrez Browser	http://www.ncbi.nih.gov/Entrez/nucleotide.html
Marshfield Comprehensive Genetic Map	http://www.marshmed.org/genetics/
Online Mendelian Inheritance in Man (OMIM)	http://www3.ncbi.nlm.nih.gov/Omim/
NCBI Gene Maps	http://www.ncbi.nlm.nih.gov/genemap/

Table II. NFJS family 1: two-point LOD scores with 17q markers[a]

Marker	Distance	Zmax $\theta = 0$	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
D17S1824	49.67 cM	–0.632	2.332	2.283	2.097	1.846	1.556	1.239	0.909	0.582	0.275	0.000
D17S798	53.41 cM	–1.813	1.223	1.258	1.156	0.998	0.804	0.593	0.378	0.183	0.045	0.000
D17S1293	56.48 cM	2.213	1.968	1.719	1.466	1.213	0.964	0.721	0.490	0.281	0.109	0.000
D17S1787	62.01 cM	4.166	3.763	3.351	2.930	2.502	2.069	1.633	1.197	0.769	0.364	0.000
D17S1868	64.16 cM	3.717	3.375	3.022	2.659	2.286	1.905	1.514	1.118	0.722	0.341	0.000
D17S1795	68.44 cM	2.941	2.638	2.329	2.014	1.698	1.380	1.066	0.758	0.464	0.202	0.000
D17S1820	71.93 cM	2.245	2.033	1.818	1.601	1.382	1.163	0.943	0.719	0.491	0.253	0.000
D17S957	80.38 cM	–0.889	2.139	2.124	1.972	1.755	1.497	1.209	0.899	0.582	0.275	0.000

[a]Sex-averaged genetic distances from 17pter in centiMorgans from the Marshfield Genetic Map.

(Monreal *et al*, 1999). The protein encoded by this gene shows domain homology to the tumor necrosis factor receptor family and it may have a receptor–ligand association with ectodysplasin-A. Nevertheless, these studies have shown that in several ectodermal dysplasia patients the underlying gene pathology involves other loci, as yet unidentified. The gene for the human DL homolog maps to 2q11–13 (Ho *et al*, 1998), distinct from our putative NFJ locus.

Two of the most striking features of individuals with the NFJ syndrome in the family described here are the lack of dermatoglyphics and the hypohidrosis. The lack of dermatoglyphics has been demonstrated in all NFJ families reported to date and is therefore the most consistent clinical feature of the syndrome. Dermatoglyphics comprise variable patterns of epidermal ridges on palmoplantar skin (Verbov, 1970). These ridges form during fetal development in the first trimester (Penrose and O'Hara, 1973; Okajima, 1975), although their development is preceded by the formation of volar pads, slight swellings of mesenchymal tissue, on the ventral apical region of the digits as well as on the interdigital, thenar, and hypothenar regions of the palms and soles at about 6–8 wk gestation (Babler, 1991). Epidermal ridges first appear at 10 wk as localized cell proliferations in the basal layer of the epidermis that form shallow primary ridges that project into the superficial dermis (Babler, 1991). The basic ridge configurations of the volar skin surfaces develop at the dermal–epidermal junction and not at the skin surface. Sweat gland/duct precursors start to appear at uniform intervals along the ridges after 14 wk, and by 17 wk, with the appearance of the stratum corneum, the configuration of the epidermal ridges resembles those of postnatal skin.

The primary defect that underlies the lack of dermatoglyphics in NFJ syndrome is unclear; however, as dermatoglyphics are preserved in other palmoplantar keratodermas, it seems likely that this is due to a developmental anomaly rather than subsequent modulation by hyperkeratosis. Therefore, we postulate that the defective protein in the NFJ syndrome is more likely to be involved in epithelial development and/or epithelial–mesenchymal interaction and is perhaps less likely to be a purely structural molecule. A number of candidate genes of this type map to the NFJ syndrome critical region, including the granulin gene (*GRN*; encoding a protein involved in epithelial growth and differentiation) (Bhandari and Bateman, 1992; Bhandari *et al*, 1992); frizzled homolog 2 (*FZD*2; a molecule involved in epithelial cell signaling pathways) (Zhao *et al*, 1995; Wang *et al*, 1996); ADAM11 (a protein implicated in cell-cell and cell–matrix interactions) (Emi *et al*, 1993); and GRB7 (a membrane bound growth factor receptor of uncertain function) (Margolis *et al*, 1992; Tanaka *et al*, 1998). Mutation analysis of these genes in the family is ongoing in the laboratory. In addition, two integrin genes, *ITGA2B* and *ITGA3B*, map to the locus. Although integrins are involved in cell adhesion and differentiation, these particular genes are expressed specifically in platelets and are therefore not good candidates. Many uncharacterized transcripts also map to the interval.

Hypohidrosis is the most debilitating aspect of the NFJ syndrome as it can lead to collapse after mild exercise. Sweat studies on two patients from the original Swiss NFJ family demonstrated a greatly reduced concentration of functional eccrine sweat glands, but those present were able to elicit normal thermoregulation (Mevorah *et al*, 1993). It is not clear, however, from that study whether the reduction in functional sweat glands was due to a general reduction in glands or whether a normal number of glands was present, of which some were nonfunctional. Light and electron microscopic studies of the dermis of these patients showed colloid–amyloid deposits around some sweat glands and deep dermal sweat ducts, inferring that these structures had undergone degeneration, thereby contributing to the hypohidrosis (Frenk *et al*, 1993). The normal thermoregulation of these patients was in contrast to other patients in the same family who were unable to sweat (Itin *et al*, 1993), thus clearly demonstrating the variation in clinical phenotype within a single pedigree. Skin biopsies from two affected individuals in our family did not show evidence of a reduced number of sweat glands and no colloid–amyloid deposits adjacent to sweat glands or ducts were identified (data not shown).

Overall, these observations of a complete lack of dermatoglyphics and variable sweat gland pathology provide evidence for a significant role for the NFJ gene in early fetal skin development. The genes encoding structural skin proteins, and the MEOX1 gene, that we assessed and sequenced in this study are all expressed in early gestation, but have been excluded as candidate genes for the NFJ syndrome. The future identification of the NFJ gene is likely to provide further insights into the regulation of fetal skin development as well as nail and tooth physiology.

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